FORMULATION OF FLOATING TABLETS OF CANDESARTAN CILEXETIL WITH INCREASED BIOAVAILIBILITY AND CONTROLLED RELEASE PROPERTY

A dissertation submitted to

THE TAMIL NADU Dr. M.G.R MEDICAL UNIVERSITY

CHENNAI – 600 032.

In partial fulfillment of the requirements for the award of the degree of

MASTER OF PHARMACY
IN
PHARMACEUTICS

Submitted by

Reg.No: 261211353

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APRIL - 2015

JAYA COLLEGE OF PARAMEDICAL SCIENCE

THIRUNINRAVUR-602024

DEPARTMENT OF PHARMACEUTICS

DATE:

This is to certify that the dissertation entitled "**Formulation of Floating Tablets Candesartan Cilexetil with increased Bioavailability and controlled release property"** Submitted by the candidate bearing Reg. No.261211353 for The Tamil Nadu Dr. M.G.R. Medical University examinations.

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(DR.N.NARAYANAN)

ACKNOWLEDGEMENT

I thank The Almighty for showering his blessings on me in completing my thesis

I express my sincere thanks to chairman **Prof.A.Kanagaraj, M.A., M.Phil, Mrs.K.Vijayakumari M.A., B.Ed** secretary**, Mr.Navaraj M.E,** Vice Chairmen, Jaya College of Paramedical Sciences for providing me all the facilities in the college.

My sincere thanks to **Dr.A.Maheswaran, M.Pharm, (Ph.D), Principal**, College of Pharmacy, Jaya College of Paramedical Sciences, for providing me all the facilities in the college and also his constant encouragement throughout the course of project work .

I owe my gratitude and sincere thanks to my guide **Dr. Narayanan,M.Pharm** Director & HOD, Department of Pharmaceutics; Jaya College of paramedical sciences, for his unstained guidance and suggestions helped me for completing my project

I express my sincere thanks to Mr,T.Munusamy Naidu, Proprietor Restech Pharma, Puducherry , for giving me an opportunity to work and learn in their organisation .

I express my sincere thanks to Prof. K.K.Narasimhalu, Prof. N.Sumathy Asst. Prof. P.Angel, Asst. Prof. B.Anitha, Asst. Prof. B.Lavanya, Asst. Prof. R.Gowri Dr.Senthilkumar, Jaya College of paramedical sciences, for their help in this work.

I am deeply thankful to The Principal Dr.R.Ealumalai, M.Sc, M.Pharm, MBA, Ph.D, Teaching staff members Mrs. A.Vijayalakshmi, Mrs.D.Kalaivani, Mrs, W.Anitha, Non Teaching Staff Mr.John Wesley, Madras College of Pharmacy, No.450, C.T.H. Road, Avadi, Chennai-54., for his suggestion in completing work.

I am deeply thankful to the Technical Assistant Mr.J.Haribabu, Jaya College Of Paramedical Sciences, for his help him in completing this work.

Last but not least I would like to thank my parents, family members for their continued support and inspiration

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1. INTRODUCTION

Oral delivery of drugs is one of the most preferable route of delivery due to the ease of administration, patient compliance and flexibility in formulation etc.[1] Controlled drug delivery systems are the delivery systems which extends the drug release and makes the drug release sustained and at predetermined rate. Floating or Gastroretentive drug delivery systems holds the advantage of both oral delivery and controlled delivery. Floating systems significantly extend the period of time, over which drug may be released and prolongs dosing intervals and increase patient compliance. These systems retain in stomach and improves the absorption window and thus enhances the bioavailability.[2]

Floating dosage forms are oral dosage forms of tablets, capsules, or micro beads and contain hydrocolloids that allow floating by swelling thereby prolong the residence time of dosage form within G.I tract.[3]

Various gastroretentive techniques were used to achieve floating concept which includes floating, swelling, high density, and bioadhesive system, have been explored to increase the gastroretention of dosage forms.[4]

Gastric emptying of dosage forms is an extremely variable process and ability to prolong and control the emptying time is a valuable asset for dosage forms, which reside in the stomach for a longer period of time than conventional dosage forms. Several difficulties are faced in designing controlled release systems for better absorption and enhanced bioavailability.[5]

Gastro retentive systems can remain in the gastric region for several hours and hence significantly prolong the gastric residence time of drugs. Prolonged gastric

retention improves bioavailability, reduces drug waste, and improves solubility for drugs that are less soluble in a high pH environment. It has applications also for local drug delivery to the stomach and proximal small intestines.

FACTORS EFFECTING GASTRIC RETENTION[6,7,8]

- **Density:** GRT is a function of dosage form buoyancy that is dependent on the density.
- **Size:** Dosage form units with a diameter of more than 7.5mm are reported to have an increased GRT compared with those with a diameter of 9.9mm.
- **Shape of dosage form:** Tetrahedron and ring shaped devices with a flexural modulus of 48 and 22.5 kilo pounds per square inch (KSI) are reported to have better GRT 90% to 100% retention at 24 hours compared with other shapes.
- **Single or multiple unit formulation:** Multiple unit formulations show a more Predictable release profile and insignificant impairing of performance due to failure of units, allow co- administration of units with different release profiles or containing incompatible substances and permit a larger margin of safety against dosage form failure compared with single unit dosage forms.
- **Fed or unfed state:** Under fasting conditions, GI motility is characterized by periods of strong motor activity or the migrating myoelectric complex (MMC) that occurs every 1.5 to 2 hours. The MMC sweeps undigested material from the stomach. However, in the fed state, MMC is delayed and GRT is considerably longer.

- **Nature of meal:** Feeding of indigestible polymers or fatty acid salts can change the motility pattern of the stomach to a fed state, thus decreasing the gastric emptying rate and prolonging drug release.
- **Caloric content:** GRT can be increased by 4 to 10 hours with a meal that is high in proteins and fats.
- **Frequency of feed:** The GRT can increase by over 400 minutes, when successive meals are given compared with a single meal due to the low frequency of MMC.
- **Gender:** Mean ambulatory GRT in males (3.4±0.6 hours) is less compared with their age and race matched female counterparts (4.6±1.2 hours), regardless of the weight, height and body surface.
- **Age:** Elderly people, especially those over 70, have a significantly longer GRT.
- **Posture:** GRT can vary between supine and upright ambulatory states of the patient.
- **Concomitant drug administration:** Anticholinergics like atropine and propantheline, opiates like codeine and prokinetic agents like metoclopramide and cisapride.
- **Biological factors:** Diabetes and Crohn's disease.

IDEAL DRUG CANDIDATES FOR FDDS[9,10]

Drugs which are suitable for floating drug delivery systems are

- Narrow absorption window in GI tract
  e.g., riboflavin and levodopa
- Primarily absorbed from stomach and upper part of GI tract
  e.g., calcium supplements, chlordiazepoxide and cinnarazine

- Drugs that act locally in the stomach
  e.g., antacids and misoprostol
- Drugs that degrade in the colon
  e.g., ranitidine HCl and metronidazole
- Drugs that disturb normal colonic bacteria
  e.g., amoxicillin trihydrate

TYPES OF FLOATING DRUG DELIVERY SYSTEMS

Floating drug delivery systems have a bulk density less than gastric fluids and so remain buoyant in the stomach with out affecting the gastric emptying rate for a prolonged period of time. While the system is floating on the gastric contents the drug is released slowly at the desired rate from the system.

Based on the mechanism of buoyancy FDDS may be classified as[11,12]

- Effervescent System
- Non- Effervescent System

EFFERVESCENT SYSTEMS

Effervescent systems reduces the density of the drug delivry system and float on the gastric fluid. It uses gas generating agents, carbonates (ex. Sodium bicarbonate) and other organic acid (e.g. citric acid and tartaric acid) present in the formulation to produce carbon dioxide (CO2) gas, thus reducing the density of the system and making it float on the gastric fluid. An alternative is the incorporation of matrix containing portion of liquid, which produce gas that evaporates at body temperature.

Volatile liquid containing systems[13,14]

The gastric residence time of a delivery system can be increased by incorporating an inflatable chamber, which contains a volatile liquid. e.g. ether, cyclopentane, that

gasifies at body temperature to cause the inflation of the chamber in the stomach. The device may also consist of a bioerodible plug made up of PVA, Polyethylene, etc.

Gas generating Systems[15,16]

These buoyant delivery systems utilize liberation of carbon dioxide from effervescent reaction between carbonate or bicarbonate salts and citric or tartaric acid. The liberated carbon dioxide gets entrapped in the hydrocolloid layer of the system. Thus the specific gravity decreases and the system begins to float.

NON-EFFERVESCENT SYSTEMS

This type of system, after swallowing, swells apparently via imbibition of gastric fluid to an extent that it prevents their exit from the stomach. These systems may be referred to as the plug-type. The air trapped by the swollen polymer confers buoyancy to these dosage forms.

Colloidal gel barrier systems[17,18]

These systems contains drug with gel forming hydrocolloids meant to remain buoyant on stomach contents. These systems incorporate a high level of one or more gel forming highly swellable cellulose type hydrocolloids. On coming in contact with gastric fluid, the hydrocolloid in the system hydrates and forms a colloidal gel barrier around the gel surface. The air trapped by the swollen polymer maintains a density less than unity and confers buoyancy to this dosage forms.

Microporous Compartment System[19,20]

This technology is based on the encapsulation of drug reservoir inside a Microporous compartment with aperture along its top and bottom wall. The peripheral walls of the

drug reservoir compartment are completely sealed to prevent any direct contact of the gastric mucosal surface with the undissolved drug. In stomach the floatation chamber containing entrapped air causes the delivery system to float over the gastric contents. Gastric fluid enters through the apertures, dissolves the drug, and carries the dissolve drug for continuous transport across the intestine for absorption.

Alginate beads[19,20]

Multiple unit floating dosage forms have been developed from freeze-dried calcium alginate. Spherical beads of approximately 2.5 mm in diameter can be prepared by dropping a sodium alginate solution in to aqueous solutions of calcium chloride, causing precipitation of calcium alginate. The beads are then separated snap and frozen in liquid nitrogen, and freeze dried at -40°C for 24 hours, leading to the formation of porous system, which can maintain a floating fource over 12 hours.

Hollow microspheres[19,20]

Hollow microspheres (microballons), loaded with ibuprofen in their outer polymer shells were prepared by a novel emulsion-solvent diffusion method. The ethanol: dichloromethane solution of the drug and an enteric acrylic polymers was poured in to an agitated aqueous solution of PVA that was thermally controlled at 40°C.The gas phase generated in dispersed polymer droplet by evaporation of dichloromethane formed in internal cavity in microspheres of the polymer with drug. The microballons floated continuously over the surface of acidic dissolution media containing surfactant for greater than 12 hours in vitro.

APPROACHES TO DESIGN OF FLOATING DOSAGE FORMS

The following dosage forms have been used for the design of single and multiple unit dosage forms:

Single unit dosage forms

In this system the globular shells apparently having low density than that of gastric fluid can be used as a carrier for drug for its controlled release. Sugar polymeric materials such as methacrylic polymer and cellulose acetate phthalate have been used to undercoat these shells. These are further coated with a drug polymer mixture. The polymer of choice can be either ethylcellulose or hydroxypropyl cellulose depending upon the type of release desired. Finally, the product floats on the gastric fluid while releasing the drug gradually over a prolonged duration.[21]

It includes incorporation of gas filled floatation chamber into a microporous component that houses a drug reservoir. Apertures or openings are present along the top and bottom walls through which the gastrointestinal tract fluid enters to dissolve the drug. The other two walls in contact with the fluid are sealed so that the undissolved drug remains therein. The fluid present can be air, under partial vacuum or any other suitable gas, liquid or solid having an appropriate specific gravity and an inert behavior. The device is of swallowable size, remains afloat within the stomach for a prolonged time and after the complete release the shell disintegrates passes off to the intestine and is eliminated.[22]

Single-unit formulations are associated with problems such as sticking together or being obstructed in the gastrointestinal tract, which may have a potential danger of producing irritation. Unfortunately floating devices administered in single unit form(HBS) are unreliable in prolonging the GRT owing to their ‘all or nothing’

emptying process and thus they may cause high variability in bioavailability and local irritation due to large amount of drug delivered at a particular site of gastrointestinal tract.[23]

Multiple -unit dosage forms

Single unit dosage forms have lot of disadvantages, hence it is needed to develop a multiple unit dosage forms. Microspheres have high drug loading capacity and many polymers have been used such as albumin, gelatin, starch, PLGA, polymethacrylate, polyacrylamine and polyalkylcyanoacrylate. spherical polymeric microsponges, also referred to as microballoons,'' have been prepared.[24] Microspheres have a characterstic internal hollow structure and show invitro flotabilty. In carbon dioxide generating multiple-unit oral formulations several devices with features that extend, unfold or are inflated by carbon dioxide generated in the devices after administration have been described in the recent patient literature. These dosage forms are excluded from the passage of the pyloric sphincter if a diameter of ~12 to 18mm in their expanded state is exceeded.[25,26]

Advantages of FDDS[27,28]

Floating dosage systems form important technological drug delivery systems with gastric retentive behavior and offer several advantages in drug delivery. These advantages include

- Improved drug absorption, because of increased GRT and more time spent by the dosage form at its absorption site.
- Controlled delivery of drugs.
- Delivery of drugs for local action in the stomach.

- Minimizing the mucosal irritation due to drugs, by drug releasing slowly at controlled rate.
- Treatment of gastrointestinal disorders such as gastro-esophageal reflux.
- Simple and conventional equipment for manufacture.
- Ease of administration and better patient compliance.

Limitations[29,30]

- The major disadvantage of floating system is requirement of a sufficient high level of fluids in the stomach for the drug delivery to float. However this limitation can be overcome by coating the dosage form with the help of bioadhesive polymers that easily adhere to the mucosal lining of the stomach.
- Floating system is not feasible for those drugs that have solubility or stability problem in gastric fluids.
- The dosage form should be administered with a minimum of glass full of water (200-250 ml).
- The drugs, which are absorbed throughout gastro-intestinal tract, which under go firstpass metabolism (nifedipine, propanolol etc.) are not desirable candidate.
- Some drugs present in the floating system causes irritation to gastric mucosa.

EVALUATION OF GASTRO RETENTIVE DOSAGE FORMS

Evaluation for gastro retention is carried out by means of X-ray or gamma scintigraphic monitoring of the dosage form transit in the GI tract.[31]

FORMULATION OF FLOATING DRUG DELIVERY SYSTEMS:

Following types of the ingredients can be incorporated in to HBS dosage form

- Hydrocolloids
- Inert fatty materials
- Release rate accelerants
- Release rate retardants
- Buoyancy increasing agents
- Miscellaneous

Hydrocolloids[32]

Hydrocolloids are synthetics, anionic or non ionic like hydrophilic gums, modified cellulose derivatives. E.g. Acacia, pectin, agar, alginates, gelatin, casein, bentonite, veegum, MC, HPC, HEC, and Na CMC can be used. The hydrocolloids must hydrate in acidic medium i.e. gastric fluid is having pH 1.2.

Acacia, pectin, gelatin, alginate, caesin etc., are generally used hydrocolloids.

These should hydrate in acidic medium i.e., in gastric fluid at a pH of 1.2.

Inert fatty materials [33]

Edible, pharmaceutical inert fatty material, having a specific gravity less than one can be added to the formulation to decrease the hydrophilic property of formulation and hence increases the buoyancy. Eg: Purified grades of beeswax, fatty acids, long chain alcohols, glycerides' and mineral oils can be used.

Edible, pharmaceutical inert fatty materials, having a specific gravity less than 1 can be added to formulation to decrease the hydrophilic property of formulation and hence increase the buoyancy. Examples: fatty acids, glycerides

Release rate accelerates[34]

The release rate of the medicament from the formulation can be modified by including excipient like lactose and/or mannitol. These may be present from about 5-60% by weight**.** The release rate of medicaments from the formulation can be modified by including excipients like lactose or mannitol.

Release rate retardant[35]

Insoluble substances such as calcium phosphate, talc, magnesium stearate decreases the solubility and hence retard the release of medicaments.

Insoluble substance such as talc, magnesium sterate decrease the solubility and hence retard the release of medicaments.

Buoyancy increasing agents[36]

Materials like ethyl cellulose can be used for enhancing the buoyancy of the formulation. Materials like ethyl cellulose, which has bulk density less than one, can be used for enhancing the buoyancy of the formulation. It may be adapted up to 80 % by weight.

Adjuvants[36]

Pharmaceutically acceptable adjuvants like preservatives, stabilizers, lubricants can be incorporated as per requirements.

ANATOMY OF GASTROINTESTINAL TRACT

The gastrointestinal tract consist of stomach, small intestine, pancreas and large intestine.

Stomach

The stomach is a 'j'-shaped organ, with two openings- oesophageal and the duodenal- and four regions- the cardia, fundus, body and pylorus. Each region performs different functions; the fundus collects digestive gases, the body secretes pepsinogen and hydrochloric acid, and the pylorus is responsible for mucus, gastrin and pepsinogen secretion.[37,38]

Small Intestine

The small intestine is the site where most of the chemical and mechanical digestion is carried out, and where virtually all of the absorption of useful materials is carried out. The whole of the small intestine is lined with an absorptive mucosal type, with certain modifications for each section. The intestine also has a smooth muscle wall with two layers of muscle; rhythmical contractions force products of digestion through the intestine (peristalisis). There are three main sections to the small intestine;

The duodenum forms a 'C' shape around the head of the pancreas. Its main function is to neutralise the acidic gastric contents (called 'chyme') and to initiate further digestion; Brunner's glands in the submucosa secrete an alkaline mucus which neutralises the chyme and protects the surface of the duodenum.[39]

The jejunum and The ileum. The jejunum and the ileum are the greatly coiled parts of the small intestine, and together are about 4-6 metres long; the junction between the two sections is not well-defined. The mucosa of these sections is highly folded (the

folds are called plicae), increasing the surface area available for absorption dramatically.[40]

Pancreas

The pancreas consists mainly exocrine glands that secrete enzymes to aid in the digestion of food in the small intestine. The main enzymes produced are lipases, peptidases and amylases for fats, proteins and carbohydrates respectively. Pancreatic exocrine secretion is hormonally regulated, and the same hormone that encourages secretion (cholecystokinin) also encourages discharge of the gall bladder's store bile. [41]

Large Intestine

The large intestine is the second to last part of the digestive system—the final stage of the alimentary canal is the anus —in vertebrate animals. Its function is to absorb water from the remaining indigestible food matter, and then to pass useless waste material from the body. [42]

The large intestine consists of the cecum and colon. It starts in the right iliac region of the pelvis, just at or below the right waist, where it is joined to the bottom end of the small intestine. From here it continues up the abdomen, then across the width of the abdominal cavity, and then it turns down, continuing to its endpoint at the anus The large intestine is about 1.5 metres (4.9 ft) long, which is about one-fifth of the whole length of the intestinal canal. [43]

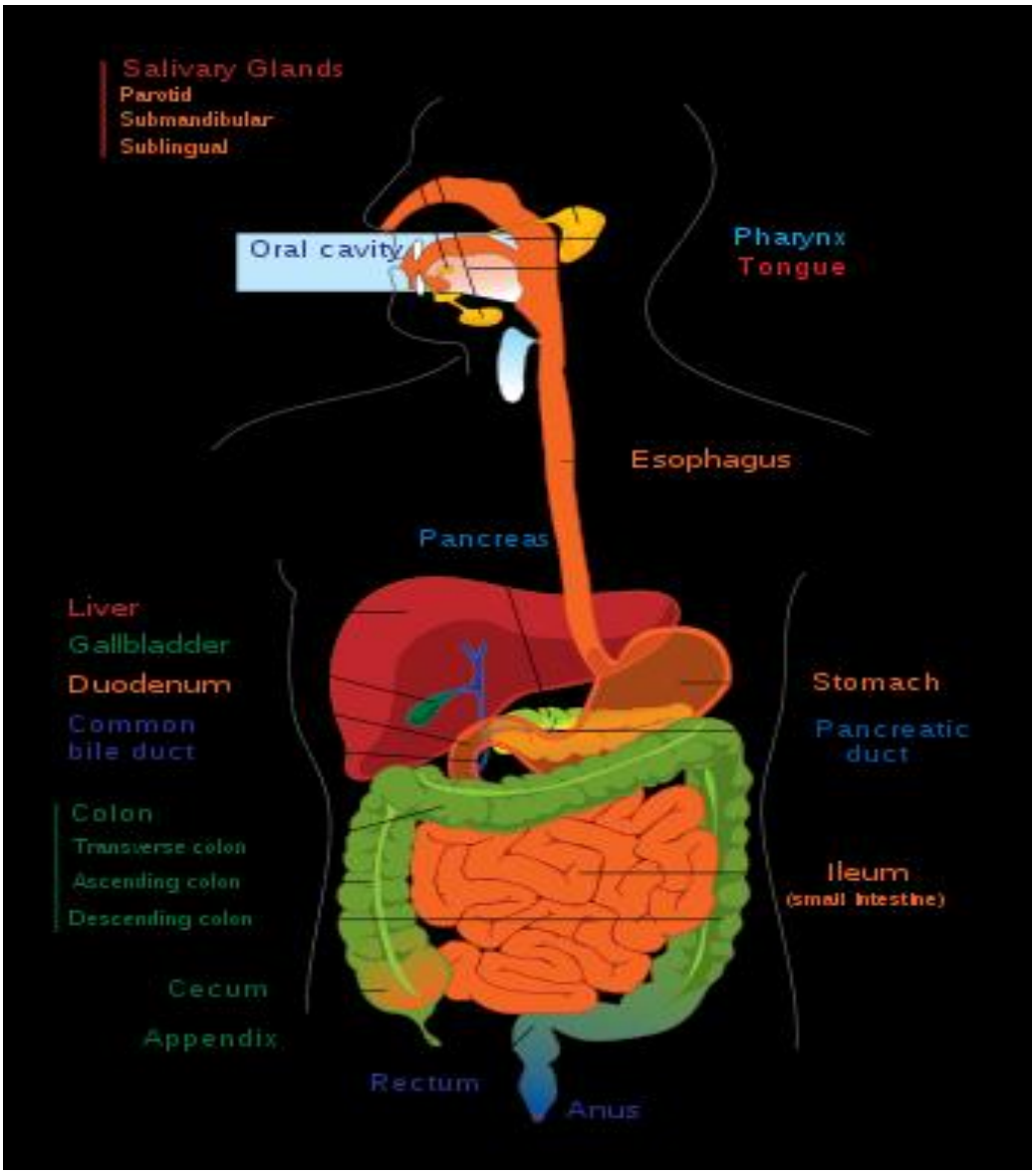

Fig 1 Anatomy of Gastrointestinal tract

PHYSIOLOGY OF GASTROINTESTINAL TRACT

Anatomically the stomach is divided into 3 regions: [44,45,46]

- Fundus
- Body and
- Antrum (pylorus).

The proximal part made of fundus and body acts as a reservoir for undigested material, whereas the antrum is the main site for mixing motions and act as a pump for gastric emptying by propelling actions.

Gastric emptying occurs during fasting as well as fed states. The pattern of motility is however distinct in the 2 states. During the fasting state an interdigestive series of electrical events take place, which cycle both through stomach and intestine every 2 to 3 hours. This is called the interdigestive myoelectric cycle or migrating myoelectric cycle (MMC), which is3.Phase III (burst phase) lasts for 4 to 6 minutes. It includes intense and regular contractions for short period. It is due to this wave that all the undigested material is swept out of the stomach down to the small intestine. It is also known as the housekeeper wave .further divided into following 4 phases, they are :

1.**Phase I** (basal phase) lasts from 40 to 60 minutes with rare contractions

2.**Phase II** (preburst phase) lasts for 40 to 60 minutes with intermittent action potential and contractions. As the phase progresses the intensity and frequency also increases gradually.

3.**Phase III** (burst phase) lasts for 4 to 6 minutes. It includes intense and regular contractions for short period. It is due to this wave that all the undigested material.

4.**Phase IV** lasts for 0 to 5 minutes and occurs between phases III and I of 2 consecutive cycles .s swept out of the stomach down to the small intestine.

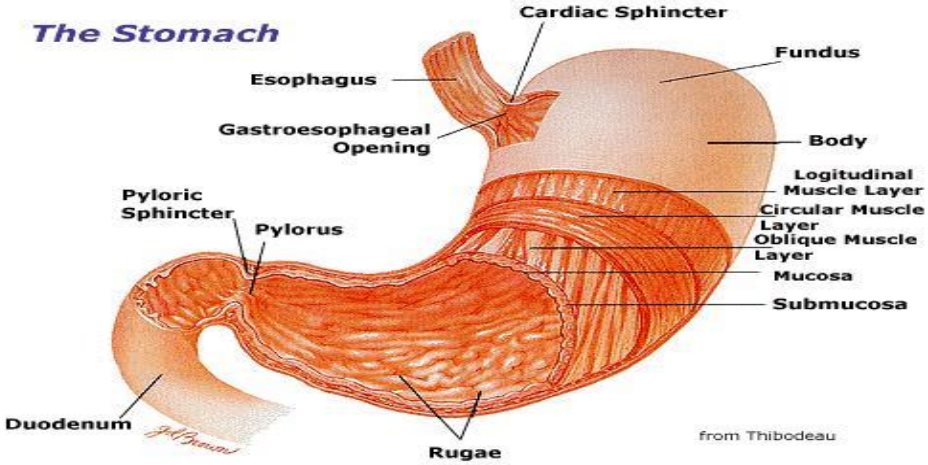

Fig2. Physiology Of Gastrointestinal Tract

2. AIM AND OBJECTIVES

Almost all drugs have side effects, this is due to toxic nature of the drug entity. Further due to the travelling or mailing of drug to one place to another place in body may produce side effects in different organs unnecessarily. So it is necessary to achieve the drug to specific targeted site. Lot of approaches is available. But most of the approaches are having practical difficulties. One of the good and significant approaches is to deliver the drug as floating tablets, which is termed as floating drug delivery systems.

The present research focused on the delivery of candesartan cilexetil via floating drug delivery system. This remains in the site of application i.e. in GIT. By this the degradation of drug is minimized. Further it may produce good therapeutic concentration in the system.

Floating drug delivery systems can remain in the gastric region for several hours and hence significantly prolong the gastric residence time of drugs. Prolonged gastric retention improves bioavailability, reduces drug waste, and improves solubility for drugs that are less soluble in a high pH environment.

Hypertension is a chronic disease condition in which the systemic arterial blood pressure is elevated. Anti-hypertensive drugs are used in the treatment of several cardiovascular disorders, particularly angina pectoris, supraventricular tachycardia and hypertension.

Candesartan Cilexetil, an antihypertensive drug competes with angiotensin II for binding at the AT1 receptor subtype. As angiotensin II is a vasoconstrictor which also stimulates the synthesis and release of aldosterone, blockage of its effects results in a decrease in systemic vascular resistance.

The present work was aimed to prepare floating tablets of Candesartan Cilexetil with increased bioavailability and controlled release property.

The overall aim and objective of the present work was to

- Formulate candesartan cilexetil floating tablets (CF1-CF6)
- Evaluation of formulated candesartan cilexetil floating tablets (CF1-CF6)

3. LITERATURE REVIEW

- **Somani VG *et al.*, (2009)[47]** developed hollow calcium pectinate beads for floating pulsatile release of aceclofenac intended for chronopharmacotherapy. Floating pulsatile concept was applied to increase the gastric residence of the dosage form having lag phase followed by a burst release. The method used for the development of the beads was a simple process of acid-base reaction during ionotropic cross linking. The floating beads obtained were porous, hollow with a bulk density < 1 and had $F_{t50}$of 14-24 h. The floating beads showed a two-phase release pattern with initial lag phase during floating in an acidic medium followed by rapid pulse in phosphate buffer.

- **Jain AK *et al.*, (2009)[48]** prepared and evaluated buoyant microspheres using famotidine as a model drug. The microspheres were prepared by solvent evaporation method using different polymers i.e., acrylcoat S 100 and cellulose acetate. The size or average diameter characterized by optical microscopy method and surface morphology was recognized by SEM.

- **Nath B *et al.*, (2009)[49]** designed a sustained release floating microcapsules of Metformin HCl using cellulose acetate butyrate and Eudragit RL100 by oil-in-oil emulsion solvent evaporation method. Polymers were used separately and in combination (1:1) to prepare different microcapsules using acetone as organic phase. FT-IR study showed no drug polymer interaction. All the prepared microcapsules showed higher amount of drug release in phosphate buffer (pH 6.8) as compared to the release in 0.1M HCl (pH 1.2).

- **Nekkanti *et al.*, (2009) [50]** developed solid oral dosage form incorporating candesartan nanoparticles by wet bead milling technique. The solid-state properties of candesartan

cilexetil before and after milling were evaluated by X-ray powder diffraction (XRPD) and differential scanning calorimetry (DSC) analysis. The milled nanosuspension was converted into solid intermediate using a spray drying process. The spray dried nanosuspensions were characterized for particle size distribution (PSD) after reconstitution to understand the impact of spray drying process on PSD. The spray dried nanoparticles were blended with excipients for tableting. XRPD and DSC analysis indicated no phase transitions. The spray dried nanoparticles showed complete recovery following redispersion in water. The rate and extent of drug dissolution in physiologically relevant dissolution medium for tablet formulation incorporating drug nanoparticles was significantly higher as compared to commercial tablet formulation. The results from dissolution studies indicated significant increase in the rate of drug dissolution in physiologically relevant dissolution medium.

- **Thamizarasi S *et al.*, (2009)**[51] prepared and evaluated poly(ε-caprolactone) microspheres of repaglinide by using solvent evaporation technique with different drug to carrier ratio. The microspheres were characterized for practical size, SEM, FT-IR study, percentage yield, drug entrapment, stability studies and *in vitro* drug release. The shape of microspheres were found to be spherical by SEM.

- **Gattani YS *et al.*, (2008)**[52] formulated and evaluated floating microparticulate oral drug delivery system of diltiazem hydrochloride. Floating microspheres were prepared by non-aqueous emulsification solvent evaporation technique using ethyl cellulose and eudragit RS-100 as the rate controlling polymer. The *in vitro* evaluation, drug-polymer compatibility,percent yield, particle size analysis, drug entrapment efficiency, *in vitro* floatability, surface topography and *in vitro* release were performed.

- **Jimenez I *et al.*, (2008)**[53] developed a sustained delivery of captopril from floating matrix tablets. The study was done using metolose SH4000/ sodium bicarbonate and at two different compaction pressures. The observation showed that the matrices compacted at lower pressure (55MPa) float in the dissolution medium for more than 8h while those compacted at 165MPa float only when sodium bicarbonate is included in the formulation. The matrix density is lower when compacted at lower pressure keep more entapped air, decreasing the agglomerate density and allowing the tablets float, on the other hand, tablets compacted at higher pressure are less porous and display a density not allowing the matrices floatation. An increasing proportion of the swelling polymer in the matrix increases. The increasing proportion of the swelling polymer in the matrix increases the maximal hydration volume as well as the time necessary to attain it. The release profiles of captopril form metolose matrices display greater percentages of drug released compared to similar matrices containing sodium bicarbonate due to an obstruction effect of the diffusion path by carbon dioxide bubbles.

- **Liu Q *et al.*, (2008)**[54] prepared a zero order delivery of a highly soluble, low dose drug Alfuzosin hydrochloride via gastro-retentive system which were prepared as two multilayer delivery systems. First formulation compressed a triple layer based on PEO while the second formulation was a bilayer composite matrix system composed of hydroxylpropylcellulose and hydroxypropylmethylcellulose. The observation showed that the systems demonstrated controlled release kinetics independent of pH changes with about 99% of dose being released around 18h. The maintenance of constant surface area during dissolution is critical for zero-order drug delivery. The burst release suppression effect brought about by raped initial swelling and controlled erosion of layers provided for programmed controlled delivery and enhanced floatation

- **Kale RD *et al.*, (2007)**[55] prepared floating drug delivery system of piroxicam microspheres using enteric polymer by emulsification technique. The microspheres remained buoyant continuously over the surface of acidic media containing surfactant for the period of 8-12 hrs in vitro. DSC and XRD studies showed that drug incorporated in the outer shell of polymer was completely amorphous. SEM indicated that the microsphere is perfect sphere with an internal hollow cavity enclosed by a rigid shell of polymer.

- **Raval JA *et al.*, (2007)**[56] prepared Ranitidine hydrochloride floating matrix tablets based on low density powder: effects of formulation and processing parameters on drug release. The absorbance of Ranitidine hydrochloride solutions was measured at 315 nm using a Shimadzu UV-1601 UV/Vis double beam spectrophotometer.

- **Gambhire MN *et al* (2007)**[57] developed floating drug delivery system of diltiazem hydrochloride using rate retardant polymers. Floating matrix tablet of diltiazem hydrochloride was prepared by direct compression method. The effect of tablet hardness on release profile was also studied. Sodium bicarbonate was used as gas generating agent. The study showed the effect of excipient on release profile of drug and use of floating controlled drug delivery.

- **Ali. J *et al*., (2007)** [58] developed a hydrodynamically balanced system of metformin as a single unit floating capsule. Various grades of low-density polymers were used for the formulation of this system. They were prepared by physical blending of Metformin and the polymers in varying ratios. The formulation was optimized on the basis of in vitro buoyancy and in vitro release in simulated fed state gastric fluid (citrate phosphate buffer pH 3.0). Effect of various release modifiers was studied to ensure the

delivery of drug from the HBS capsules over a prolonged period. Capsules prepared with HPMC K4M and ethyl cellulose gave the best in vitro percentage release and was taken as the optimized formulation. In vivo studies were carried out in rabbits to assess the buoyancy, as well as the pharmacokinetic parameters of the formulation using gamma scintigraphy.

- **Bardonn *et al.*, (2006)**[59] The challenge to develop efficient gastroretentive dosage forms began about 20 years ago, following the discovery of Helicobacter pylori by Warren and Marshall. In order to understand the real difficulty of increasing the gastric residence time of a dosage form, we have first summarized the important physiologic parameters, which act upon the gastric residence time. Afterwards, we have reviewed the different drug delivery systems designed until now, i.e. high-density, intragastric floating, expandable, superporous hydrogel, mucoadhesive and magnetic systems.

- **Patil JM *et al.*, (2006)**[60] investigated rate controlled drug delivery system to solve physiological problems, such as short gastric residence time (GRT) and unpredictable gastric emptying times. Prolonged GRT may widen the stomach potential as the drug absorbing organ. Several approaches are currently utilized in GRT, floating drug delivery system (FDDS), swelling and expanding systems, polymorphic bioadhesive systems, modified shape systems, high density systems and other delayed gastric emptying devices were discussed in detail.

- **Arora S *et al.*, (2005)**[61] investigated floating drug delivery systems (FDDS) to compile the recent literature with special focus on the principal mechanism of floatation to achieve gastric retention. The recent developments of FDDS including the physiological and formulation variables affecting gastric retention, approaches to

design single-unit and multiple-unit floating systems, and their classification and formulation aspects are covered in detail. This review also summarizes the in vitro techniques, in vivo studies to evaluate the performance and application of floating systems, and applications of these systems. These systems are useful to several problems encountered during the development of a pharmaceutical dosage form.

- **Wei *et al*., (2004)**[62] developed a pH dependent floating sustained release tablet for gastric retention of 5-FU and prepared two layer floating tablet wherein floating ability is independent of the gastric acidity variation.

- **Li *et al*., (2003)**[63] investigated the effect of formulation variables on the calcium release and floating properties of the delivery system by using 2x3 factorial designs by using different grades of Hydroxypropylmethylcellulose (K100LV and K4M) and carbopol. They reported that by increasing the HPMC viscosity the release rate decreases and floating properties improved as the viscosity of the polymer is increased. Carbopol (CP934) incorporation was found to compromise the floating capacity of floating and release of calcium.

- **Umamaheswari RB *et al.*, (2002)**[64] prepared floating microspheres containing the antiurease drug acetohydroxamic acid (AHA) by a novel quasi-emulsion solvent diffusion method. The microballons were coated with 2% w/v solution of polycarbophil by the air suspension coating method. The bioadhesive property of the microspheres was investigated by the detachment force measurement method. In vitro growth inhibition studies were performed in isolated *H. pylori* culture. The results suggest that AHA-loaded floating microspheres are superior as potent urease inhibitors whereas urease plays an important role in the colonization of *H. pylori*.

- **Joseph NJ *et al.*, (2002)[65]** prepared floating type dosage form of piroxicam in hollow polycarbonate (PC) microspheres capable of floating on simulated gastric and intestinal fluids was prepared by a solvent evaporation technique. Incorporation efficiencies of over 95% were achieved for the encapsulation. In vitro release of piroxicam from PC microspheres into simulated gastric fluid at 37ºC showed no significant burst effect. The amount released increased with time for about 8 h after which very little was found to be released up to 24 h. In intestinal fluid, the release was faster and continuous and at high drug payloads, the cumulative release reached above 90% in about 8 h.

- **Zhang J *et al*., (2000)[66]** developed floating tablets of Captopril using HPMC K4M and K15M and Carbopol 934P. Study was concluded that buoyancy of tablet is governed by both the swelling of the hydrocolloid particles on the tablet surface when it contacts the gastric fluids and the presence of internal voids in the center of the tablet.

- **Iannuccelli *et al*., (2000)[67]** used PVP solid dispersions for the controlled release of furosemide from a floating multiple-unit system. Furosemide has "absorption window" in the upper gastrointestinal tract. So it was necessary to increase gastric residence time for furosemide. The complete dose release over the actual intra-gastric residence time of the system (about 8 hr) was achieved by loading both the core and the membrane forming the units with 1:5 furosemide: PVP solid dispersion. Physicochemical analysis suggested that amorphous state of furosemide enhanced drug solubility and dissolution rate, which led to the desired release profile from the floating units.

- **Ozdemir *et al*., (2000)[68]** developed floating bilayer tablet of furosemide- cyclodextrin inclusion complex. They determined the gastric residence time using radiographs by

adding $BaSO_4$ and reported that the tablet stayed in stomach for 6 hours. Also the bioavailability of furosemide from floating tablet was about 1.8 times that of the conventional tablet and also significant *in vitro – in vivo* correlation was detected.

- **Krogel and Bodmeier (1999)[69]** developed and evaluated floating drug delivery system based on effervescent core and a polymeric coating. The mechanical properties (puncture strength and elongation) of acrylic (Eudragit RS, RL and NE) and cellulose (cellulose acetate, ethyl cellulose) polymer, which primarily determined the type of delivery system, a polymer coating with a high elongation value and high water low carbon dioxide permeability was selected (Eudragit RL/ acetyl tributyl citrate 20%w/w) in order to initiate the effervescent reaction and the floating process rapidly. HPMC was also added in the core to retard drug release. The composition and hardness of the tablet core and the composition and hardness of the coating could control the time of flotation.

- **Lee *et al.*, (1999)[70]** prepared floating acrylic resin microspheres with an internal hollow structure by a solvent diffusion and evaporation method. The yield of microspheres depended on the diffusion rate of ethanol and/or isopropanol in the gastric phase. Best results were obtained at the volume ratio of Ethanol: Isopropanol: dichloromethane (8:2:5). When a drug had low solubility in dichloromethane, the loading efficiency was the lowest.

- **Chen and Hao (1998)[71]** studied the *in vitro* performance of floating sustained release capsule of verapamil. Capsules filled with mixture of verapamil, HPC and effervescent materials are proposed to provide floating and sustained release for over 10 hrs. The effects of weight filled in the capsule, amount of HPC and the addition of effervescent

material on the dissolution kinetics were studied. They concluded that the release of Verapamil from the capsule followed Higuchi release model. However, when effervescent material was added, the system showed a zero-order release.

- **Gerogiannis *et al.*, (1993)**[72] examined the floating and swelling characteristics of several excipients used in controlled release technology. The floating behavior was evaluated with resultant weight measurements, while a gravimetric method was employed for studying their swelling. The results indicated that higher molecular weight polymers had slower rates of polymer hydration and usually followed by enhanced floating behavior.

- **Oth M *et al.*, (1992)**[73] developed bilayer floating dosage unit to achieve local delivery of Misoprostal. The system was capsule consisting of a floating layer maintaining the dosage unit buoyant upon the gastric content and drug layer formulated to act as a sustained delivery system. The differential design of the two layers allows the optimization of both floating capability and drug release profile.

- **Desai and Bolton (1993)**[74] developed controlled release floating tablets of the theophylline using agar and light mineral oil. Tablets were made by dispersing drug and mineral oil mixture in a warm agar solution. The resultant mixture was poured into tablets moulds, which on cooling and air-drying formed floatable CR tablets. The light mineral oil was essential for the floating property of the tablets since relatively high amount of the drug (75%) was used.

DRUG PROFILE

CANDESARTAN CILEXETIL[75-80]

Name

Candesartan cilexetil

Colour

White to off white

IUPAC Name

2-ethoxy-3-[[4-[2-(2H-tetrazol-5yl)phenyl]phenyl]methyl]benzimidazole-4-carboxylic acid

Molecular Formula

C24H20N6O3

Chemical Structure

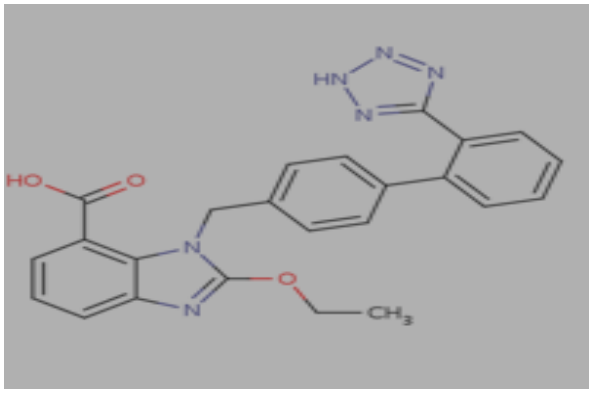

Fig 3. Structure of candesartan cilexetil

Molecular Weight

610.659660 [g/mol]

Melting Point

163^0C

Solubility

Sparingly soluble in methanol, insoluble in water

PHARMACOLOGY

Mechanism of Action

Candesartan competes with angiotensin II for binding at the AT1 receptor subtype. As angiotensin II is a vasoconstrictor which also stimulates the synthesis and release of aldosterone, blockage of its effects results in a decrease in systemic vascular resistance.

PHARMACOKINETICS

Bioavailability

15%

Distribution

V_d is 0.13 L/kg

Metabolism

Candesartan cilexetil is bioactivated by ester hydrolysis during absorption from the GI tract to candesartan. Candesartan undergoes minor hepatic metabolism by O-deethylation to an inactive metabolite.

Elimination

Primarily as unchanged drug in the urine and by the biliary route, in the feces. Plasma Cl is 0.37 mL/min/kg. Renal Cl is 0.19 mL/min/kg. 26% is excreted unchanged in urine.

Half Life

Approximately 9 hrs

THERAPEUTIC USES

Candesartan cilexetil is used to treat hypertension.

ADDITIVES PROFILE

SODIUM BICARBONATE[81,82]

Chemical Name

Carbonic acid monosodium salt

Formula:

$NaHCO_3$

Physical and chemical properties

Molecular weight	**:**	84.01
Colour	**:**	White
Nature	**:**	Crystalline powder
Odour	**:**	Odourless
Taste	**:**	Saline/slight alkaline
Density	**:**	0.869-2.173 g/cm^3
Moisture content	**:**	less than 1%w/w
Solubility	**:**	Soluble in water, practically insoluble in ethanol (95%) and ether.
Melting point	**:**	270 °C (with decomposition)

Functional category

Alkalizing agent, therapeutic agent

Applications

- Used in pharmaceutical formulation as a source of carbon dioxide in effervescent tablets and granules.
- Used to produce or maintain an alkaline pH in a preparation, like solution of Erythromycin, Lidocaine, and Niacin etc.

- Used to produce a sodium salt of the active ingredient that has enhanced solubility.
- Used as a freeze-drying stabilizer and in toothpaste.

Stability and Storage

Sodium bicarbonate is stable in dry air but slowly decomposed in moist air and should therefore be store in well-closed container in a cool dry place.

Safety

Orally ingested sodium bicarbonate neutralizes gastric acid with the evolution of carbon dioxide and may cause stomach cramps and flatulence (Rowe et al., 2003).

POLY VINYL PYROLIDONE K-30[81,82]

Chemical Name

1-Ethenyl-2-pyrrolidinone homopolymer

Empirical Formula

$(C_6H_9NO)_n$

Molecular Weight

50 000

Structural Formula

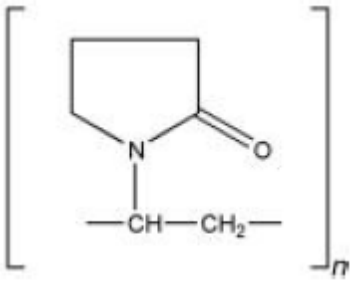

Fig 4. Structure of PVP K30

Functional Category

Disintegrant; dissolution aid; suspending agent; tablet binder.

Description

It occurs as a fine, white to creamy-white coloured, odourless or almost odourless, hygroscopic powder. It is manufactured by spray-drying and occurs as spheres.

Flowability

16 g/s.

Melting point

150°C.

Moisture content

Very hygroscopic, significant amounts of moisture being absorbed at low relative humidities.

Applications

It is primarily used in solid-dosage forms. In tableting, povidone solutions are used as binders in wet-granulation processes. Povidone is also added to powder blends in the dry form and granulated *in situ* by the addition of water, alcohol, or hydroalcoholic solutions. Povidone is used as a solubilizer in oral and parenteral formulations and has been shown to enhance dissolution of poorly soluble drugs from solid-dosage forms.

ETHYL CELLULOSE[81,82]

Synonyms

Aqualon, Ethocel, Surelease

Chemical name

Cellulose ethyl ether

Application

Ethyl cellulose is widely used as coating agent, , tablet binder, tablet filler and viscosity-increasing agent. The main use of ethyl cellulose in oral formulations is as hydrophobic coating agent for tablets and granules. Ethyl cellulose coatings are used to modify the release of a drug, to mask an unpleasant taste or to improve the stability of formulations.

Solubility

Ethyl cellulose is practically insoluble in glycerin, propylene glycol and water. It is soluble in chloroform, methyl acetate, dichloromethane and tetrahydrofuran. But soluble in mixtures of 20 parts of ethanol (96 %) and 80 parts of toluene (w/w).

Description

Ethyl cellulose is tasteless, white to light tan-coloured powder, free-flowing

pH

The pH of a 2 % w/w aqueous suspension is 5-7.5.

Viscosity

A wide range of viscosity type of ethyl cellulose is available. The range of viscosities is nominally from 7 to 100 mPa s (7-100cP).

Stability

Ethyl cellulose is stable powder, it is slightly hygroscopic. .It is chemically résistance to alkalies, both dilute and concentrated. Ethyl cellulose is subject to oxidative degradation in the presence of sunlight or UV light at elevated temperatures should be stored at a temperature not exceeding 32 degrees in a dry area away from all sources of heat.

HYDROXYPROPYL METHYLCELLULOSE(HPMC) [81,82]

Synonyms

Methocel, Methylcellulose, cellulose, hydroxypropylmethyl ether, hypromellose

Molecular weight

Ranges between 10000 to 1500000

Description

Odourless, tasteless, creamy white powder

Solubility

Soluble in cold water, practically insoluble in Chloroform, ethanol (95%) and ether but Soluble in mixture of ethanol and Dichloromethane.

Viscosity

HPMC-K4M-3,000-5600mPas**,** K15M: 12,000-21,000mPas, K100M: 80,000-1, 20,000mPas

Melting point

Browns at 190-200 °C.

Functional Category

Coating agent, film-forming, rate-controlling polymer for sustained release, stabilizing agent, suspending agent, tablet binder, viscosity-increasing agent.

Application

- In oral product HPMC is primarily used as tablet binder, in film coating and as an extended release tablet matrix. Concentration between 2-5% w/w may be used as a binder in either wet or dry granulation process. High viscosity grade may be used to retard the release of water-soluble drug from a matrix.
- HPMC is widely used in oral and topical pharmaceutical formulation.

- Concentration of 0.45-1% w/w may be added as a thickening agent to vehicle for eye drop and artificial tear solution.
- HPMC is used as an adhesive in plastic bandage and as a wetting agent for hard contact lenses. It is widely used in cosmetics and food products.
- In addition, HPMC is used as an emulsifier, suspending agent and stabilizing agent in topical gels and ointments. As a protective colloid, it can prevent droplets and particle from coalescing or agglomerating thus, inhibiting the formation of sediments.

Stability and storage

It is stable although it is slightly hygroscopic. The bulk material should be stored in an airtight container in a cool and dry place. Increased in temperature reduces the viscosity of the solution.

CARBOPOL 934[81,82]

Synonyms

Acritamer; acrylic acid polymer; Carbopol; carboxy polymethylene, polyacrylic acid; carboxyvinyl polymer; Pemulen; Ultrez.

Chemical Name

Carbomer

Molecular Weight

$3x10^6$D

Functional Category

Bio adhesive, emulsifying agent, suspending agent, tablet binder, viscosity increasing agent, release modifying agent.

Applications

Carbopol 934 is used mainly in liquid or semisolid pharmaceutical formulations as suspending or viscosity increasing agent. Formulation including Creams, gels and ointments for in ophthalmic rectal and topical preparations. In the tablet formulations carbomers are used as dry or wet binder and as a rate controlling excipients.

Carbomer rasines have also been investigated in the preparation of sustained release matrix beads, as enzyme inhibitors of intestinal proteases in peptide containing dosage forms, as a bioadhesive patch for cervical patch and for intranasally administered microspears, in magnetic granules for site specific drug delivery to the esophagus and in oral mucoadhesive controlled drug delivery system

Stability

Carbopol is stable and should be stored in tight containers.

Incompatibilities

Carbomer are discolored by resorcinol and are incompatible with phenol, cationic polymers strong acids and high level of electrolyte

XANTHAM GUM[81,82]

Synonyms

Corn sugar gum; E415; Xantural; Rhodigel

Chemical name

Xanthan gum.

Molecular Weight

2000000

Description

Cream or white-colored odorless free flowing fine powder.

Solubility

Practically insoluble in ethanol and ether. Soluble in cold or warm water.

Viscosity

The viscosity of xantham gum solution is considerably increased or gelation occurs, in the presence of some materials such as ceratonia, guar gum and magnesium aluminium silicate.

Incompatibilities

Xantham gum is an anionic material and is not usually compatible with cationic surfactants as precipitation occurs. Xantham gum is compatible with most synthetic and natural viscosity increasing agents.

Functional Category

Viscosity increasing agent, suspending agent.

Applications

Xantham gum is widely used in oral and topical pharmaceutical formulations. It is used as Viscosity increasing agent, suspending agent, and also has been used to prepare sustained release matrix tablets.

Stability

It is a stable material. The bulk material should be stored in a well closed container in a cool, dry place.

MAGNESIUM STEARATE[81,82]

Synonyms

Magnesium octadecanoate; octadecanoic acid, magnesium salt; stearic acid, magnesium salt.

Chemical Name

Octadecanoic acid magnesium salt

Empirical formula

C36H70MgO4

Molecular Weight

591.34

Structural formula

[CH3(CH2)16COO]2Mg

Category

Tablet and capsule lubricant.

Description

A very fine, light white, precipitated or milled, impalpable powder of low bulk density, having a faint odor of stearic acid and a characteristic taste. The powder is greasy to the touch and readily adheres to the skin.

Solubility

Practically insoluble in ethanol, ethanol (95%), ether and water; slightly soluble in warm benzene and warm ethanol (95%).

Applications

Widely used in cosmetics, foods, and pharmaceutical formulations. As a lubricant in capsule and tablet manufacture at concentrations between 0.25% and 5.0% w/w. Also used in barrier creams.

TALC[81,82]

Synonyms

Altalc; E553b; hydrous magnesium calcium silicate; hydrous magnesium silicate; Luzenac Pharma; magnesium hydrogen metasilicate; Magsil Osmanthus; Magsil Star; powdered talc; purified French chalk; Purtalc; soapstone; steatite; Superiore

Chemical Name

Talc

Empirical formula

Mg6 (Si2O5)4(OH) 4

Category

Glidant; tablet and capsule diluent; tablet and capsule lubricant.

Description

Very fine, white to grayish-white, odorless, impalpable, unctuous, crystalline powder. It adheres readily to the skin and is soft to the touch and free from grittiness.

Solubility

Insoluble in dilute acids and alkalis, organic solvents, and water.

Incompatibilities

Incompatible with quaternary ammonium compounds.

Applications

Used as a dissolution retardant in the development of controlled-release products, as a lubricant in tablet formulations; in a novel powder coating for extended-release pellets, and as an adsorbant.

4. PLAN OF WORK

PREFORMULATION STUDIES

- **Drug – Additives Compatibility Study**
  - Fourier Transform Infra-Red (FTIR) Study
- **Evaluation of flow properties of Powder Blends:-**
  - Angle of Repose
  - Bulk Density
  - Tapped Density
  - Compressibility Index
  - Hausner's Ratio

FORMULATION STUDIES

Formulation of candesartan cilexetil floating tablets (CF1- CF6)

EVALUATION STUDIES

- Weight variation
- Thickness
- Hardness
- Friability
- Assay
- Floating lag time
- Floating time
- In vitro release

5. MATERIALS AND METHODS

Table 1 List of Materials

S.No.	MATERIAL	SOURCE
1	Candesartan cilexetil	Aurobindo pharma Pvt Ltd, Hyderabad
2	Carbopol934	Biochemika reagents
3	HPMC	Otto reagents
4	Xanthum gum	SD Fine Chemicals Ltd
5	Tartaric acid	Spectrum reagents, cochin
6	Sodium bicarbonate	Sisco research laboratories pvt ltd, Mumbai
7	Potassium bromide (IR grade)	Merck, Goa
8	Potassium dihydrogen sulphate	Central drug house (p) ltd, mumbai
9	Sodium chloride	Sisco research laboratories pvt ltd, Mumbai
10	Potassium chloride	Sisco research laboratories pvt ltd, Mumbai
11	PVPK-30	Sisco research laboratories pvt ltd, Mumbai
12	Lactose	Otto reagents
13	Talc	Otto Chemika-Biochemika reagents
14	Magnesium Stearate	Loba chemie pvt, ltd,mumbai
15	Hydrochloric Acid	Merck specialties Pvt Ltd, Mumbai
16	Methanol	Loba chemie pvt ,ltd,Mumbai
17	Acetone	Sisco research laboratories pvt ltd, Mumbai
18	Ethanol	Loba chemie pvt ,ltd,mumbai

Table 2 List of Equipment Used

S.No	INSTRUMENTS	SOURCE
1	Tablet compression machine	Cadmach, Ahmedabad.
2	Mechanical sieve shaker	Hicon, grover enterprises New Delhi.
3	Hot air oven for drying	Hicon, grover enterprises New Delhi.
4	Electronic weighing balance	Shimadzu, Japan.
5	FTIR	Alphar T0, Bruker, New Delhi
6	Dissolution tester	Electro lab TDT- 08L
7	UV- spectrophotometer	UV-1700, Shimadzu, Mumbai
8	Hardness tester	Monsanto
9	Bulk density apparatus	Electro lab
10	Friabilator	Electrolab, Mumbai.
11	pH meter	L I 120, Elico India Pvt ltd.

METHODS

PREFORMULATION STUDIES

Standard curve of candesartan cilexetil[83]

The λ max of candesartan cilexetil in 0.1 N HCl was scanned to be 210 nm using UV spectrometer. The drug was dissolved in required quantity of 0.1N HCl and the volume was made 100 ml using 0.1N HCl. From this stock solution series of concentration was prepared. From the above solutions 2,4,6,8,10 ml was taken to dilute to 10ml using 0.1N HCl to obtain the concentration of 2,4,6,8,10µg/ml.

Drug-excipient compatibility studies[84,85]

- ***IR Spectroscopy***

IR spectra of pure candesartan cilexetil, additives and combination of candesartan cilexetil with additives were obtained by using Perkin-Elmer Fourier transform infrared spectrophotometer using KBr pellets. KBr pellets were prepared by gently mixing the sample with KBr. The scanning range used was 4000 to 400cm^{-1}.

The results were given in results and discussion section.

Angle of repose[86]

It was measured by fixed funnel technique. In this technique a funnel containing aceclofenac was kept at a fixed height, and it was allowed to flow to the surface which contains graph paper. This is due to gravitational force. The height and radius of the heap formed was measured. The formula for angle of repose (θ) was

$$\theta = \tan^{-1}(h/r)$$

The results were recorded and given in results and discussion.

Bulk density & Tapped density[87]

Bulk densities of granules were determined by pouring gently 20 gm of sample through a glass funnel into a 100 ml graduated cylinder. The volume occupied by the sample was recorded. Bulk density and tapped density were calculated by the formula

$$\text{Bulk Density} = \frac{\text{Mass of Powder}}{\text{Volume of Powder (Untapped)}}$$

$$\text{Tapped Density} = \frac{\text{Mass of Powder}}{\text{Volume of Powder (Tapped)}}$$

The results were recorded and given in the results and discussion.

Compressibility Index[87]

CI of the powder was determined from the bulk and tap density as follows[4]

$$\text{Percentage Compressibility Index} = 100 \text{ X } \frac{(\text{Tapped Density - Bulk Density})}{\text{Tapped Density}}$$

The results were recorded and given in the results and discussion.

Hausner's ratio[87]

It was calculated as

$$\text{Hausner ratio} = \frac{\text{Tapped Density}}{\text{Bulk Density}}$$

FORMULATION OF CANDESARTAN CILEXETIL FLOATING TABLETS (CF1 – CF6)

Table 3 Formula for candesartan cilexetil floating tablets (CF1 – CF6)

S.No	Ingredients	CF1 (mg)	CF2 (mg)	CF3 (mg)	CF4 (mg)	CF5 (mg)	CF6 (mg)
1	Candesartan cilexetil	30	30	30	30	30	30
2	HPMC	100	-	-	50	50	-
3	Carbopol 934	-	100	-	50	-	50
4	Xanthum gum	-	-	100	-	50	50
5	Tartaric acid	30	30	30	30	30	30
6	Sodium bicarbonate	30	30	30	30	30	30
7	Lactose	10	10	10	10	10	10
8	Magnesium stearate	5	5	5	5	5	5
9	Talc	5	5	5	5	5	5
Weight of the tablet (mg)		**210**	**210**	**210**	**210**	**210**	**210**

Candesartan cilexetil floating tablets were prepared by direct compression method. Accurately weighed quantities of additives were placed in a mortar and mixed well gradually with constant kneading to ensure homogenous mass. The granules were lubricated with 1 % magnesium stearate and finally again lubricated with talc. Finally the lubricated granules were directly compressed into tablets on a tablet punching machine.

EVALUATION OF CANDESARTAN CILEXETIL FLOATING TABLETS

Weight variation

Twenty tablets were selected at random and the average weight was determined. Not more than two of the individual weights deviate from the average by more than the percentage shown in table below and none deviates by more than twice that percentage.[88]

The results were given in results and discussion section.

Thickness

Thickness of the tablet is measured by using Vernier caliper.

The results were given in results and discussion section.

Hardness

Hardness was measured using Pfizer hardness tester which measure the pressure required to break the diametrical placed tablets by the pressure with coiled spring.[89,90]

The results were given in results and discussion section.

Friability

Twenty tablets were weighed and placed in the friabilator. The initial weight, final weight and the individual weight of the tablets were determined. The friability was

determined as the percentage loss in the weight of the tablets. A loss of less than 0.5 to 1% in weight is generally considered acceptable.[91]

The results were given in results and discussion section.

Content uniformity

It is the amount of drug present in each tablets. Twenty tablets were weighed and powdered. 0.05gm equivalent to candesartan cilexetil was weighed and transferred into 100ml volumetric flask, dissolved and volume made upto 100ml. From this solution 5 ml was to diluted to 50ml with 0.1N HCl. The absorbance was measured at 210nm using UV spectrophotometer.[92]

The results were given in results and discussion section.

Floating lag time

The floating lag time is determined in order to assess the time taken by the dosage to float on the top of the dissolution medium, after placing the dosage form in the medium. The time required to float is noted. [93]

The results were given in results and discussion section.

Floating time

It is the time the tablet constantly floats on the dissolution medium (i.e duration of floating) in the dissolution medium. [93]

The results were given in results and discussion section.

Dissolution studies[94]

The dissolution medium used was 0.1N HCl. 900ml of dissolution medium was used in each dissolution vessel and paddle type apparatus was used. The temperature maintained at temperature 37± 0.5^0C and rotated at 75 rpm. The tablets of candesartan cilexetil were placed in dissolution medium. About 5ml of the dissolution medium was pipetted out for every sampling time and the volume was adjusted using by replacing with 5ml of 0.1N HCl. The samples collected in volumetric flask and the volume was made up to 10ml with 0.1N HCl. The drug content was identified by the usual method given in drug content section.

6. RESULTS AND DISCUSSION

PREFORMULATION STUDIES

Standard Graph of Candesartan Cilexetil

Table 4 Standard graph of Candesartan cilexetil

S. No.	Concentration (µg/ml)	Absorbance
1	0	0.000
2	2	0.072
3	4	0.138
4	6	0.189
5	8	0.274
6	10	0.365

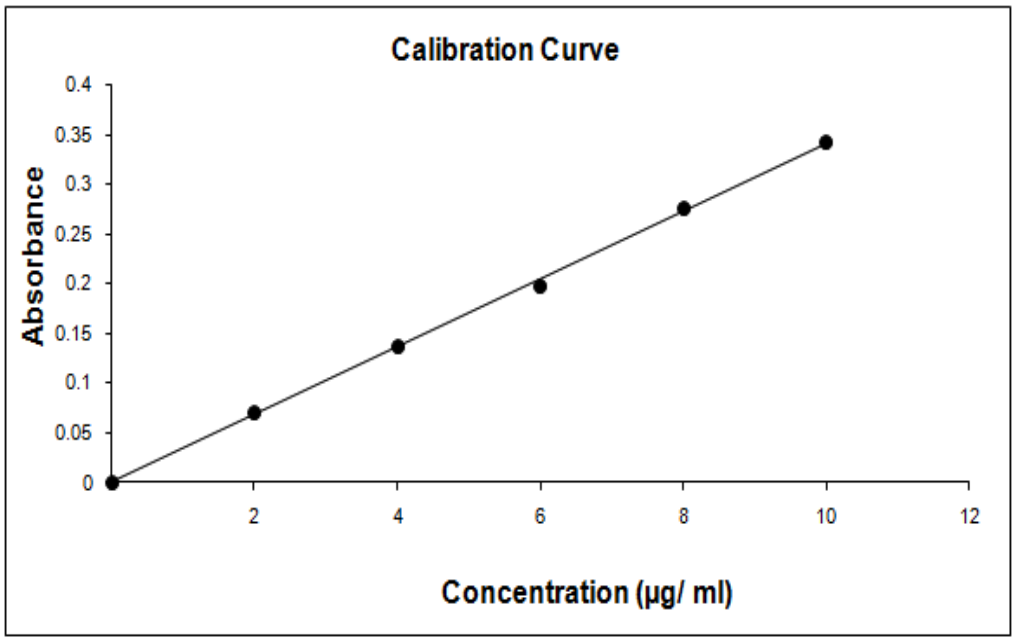

Fig 5. Standard graph of candesartan cilexetil in 0.1N HCl

From the graph it indicated that the concentration –absorbance curve for candesartan cilexetil followed the Beer Lambert's law.

Compatibility studies

FTIR studies

The FTIR graphs for the candesartan cilexetil and candesartan cilexetil with additives were given below.

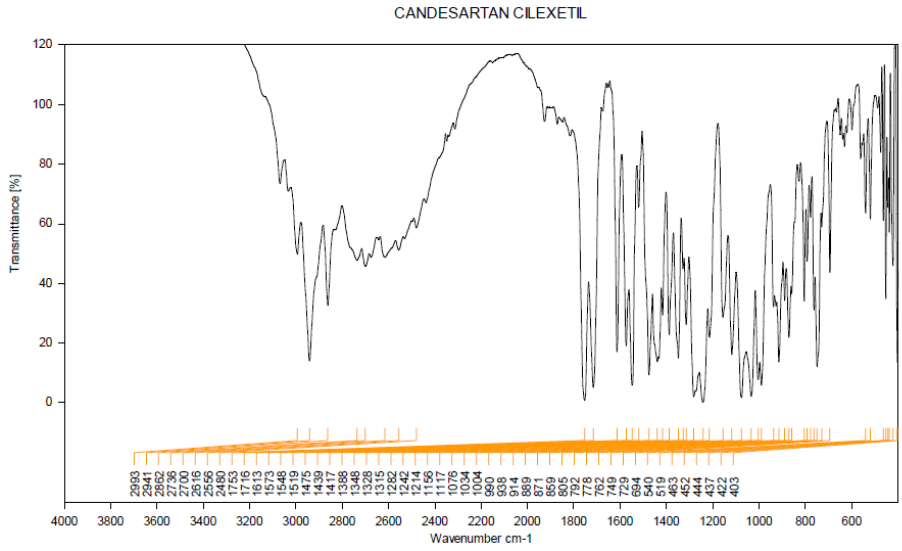

Fig 6. FTIR of candesartan cilexetil

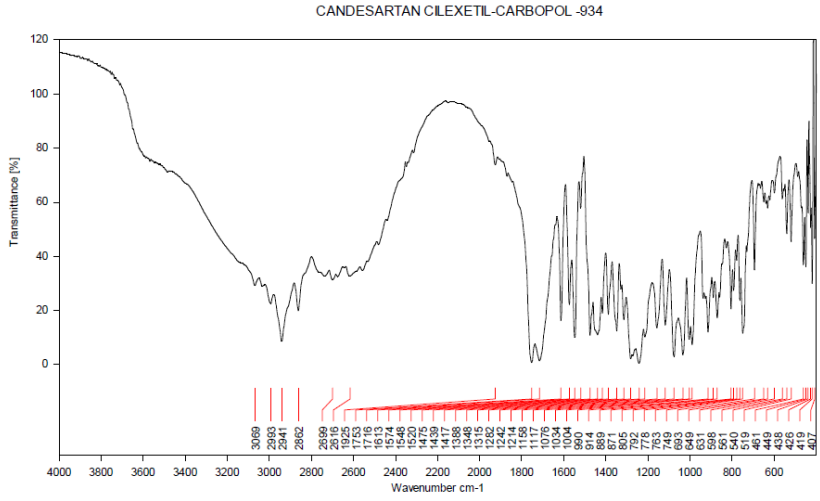

Fig 7. FTIR of candesartan cilexetil + carbopol 934

From the above FTIR graphs it was concluded that candesartan cilexetil has no interaction with additives.

EVALUATION OF BLEND

Table 5 Flow properties – angle of repose, bulk density and tapped density

Formulation	Angle of repose(θ)	Bulk density (gm/cm^3)	Tapped density (gm/cm^3)
CF1	23.60±0.40	0.26±0.03	0.34±0.03
CF2	22.72±0.48	0.37±0.02	0.42±0.06
CF3	22.56±0.50	0.35±0.04	0.36±0.01
CF4	22.64±0.50	0.28±0.02	0.33±0.03
CF5	22.92±0.45	0.28±0.02	0.48±0.02
CF6	23.42±0.42	0.26±0.02	0.31±0.02

Table 6 Flow properties – Carr's index and Hausner's ratio

Formulation	Carr's index (%)	Hausner's ratio
CF1	15.06±0.01	1.17±0.01
CF2	26.06±0.01	1.37±0.02
CF3	15.39±0.06	1.11±0.03
CF4	15.02±0.03	1.17±0.04
CF5	8.57±0.04	1.14±0.05
CF6	18.39±0.01	1.24±0.02

From the values of the angle of repose, bulk density, tapped density, carr's index and Hausner's ratio it was found that almost all granules for the formulation possessed good flow property.

EVALUATION OF FLOATING TABLET

Weight variation:

The total weight of each formulation is not maintained constant but the weight variation is in the range of ± 5% w/w indicating good control of compression process

Table 7 Weight Variation

S.NO.	FORMULATIONS	WEIGHT VARIATION(mg)
1	CF1	210±0.04
2	CF2	210±0.02
3	CF3	210±0.02
4	CF4	210±0.02
5	CF5	210±0.03
6	CF6	210±0.02

From the weight variation results it was found that there is no loss in manufacturing process which indicated that the process followed is good.

Friability

The friability was determined as the percentage loss in the weight of the tablets. A loss of less than 0.5 to 1% in weight is generally considered acceptable.

Table 8 Percentage Friability

S.NO	FORMULATIONS	FRIABILITY (%)
1	CF1	0.27±0.12
2	CF2	0.37±0.16
3	CF3	0.52±0.14
4	CF4	0.53±0.22
5	CF5	0.21±0.13
6	CF6	0.22±0.12

From the results of friability, it was found that all the trials were successful and passed the quality control test for friability.

Hardness & Thickness

Table 9 Hardness & Thickness

S.No	Formulations	Hardness (Kgs)	Thickness (mm)
1	CF1	4.5±0.20	3.0±0.1
2	CF2	5.2±0.12	2.9±0.5
3	CF3	4.6±0.11	3.1±0.2
4	CF4	5.2±0.16	3.2±0.2
5	CF5	5.5±0.09	3.0±0.2
6	CF6	6.8±0.04	2.9±0.1

From the results of Hardness and Thickness it was found that the all formulations prepared were possessing suitable hardness and thickness. All of the trials comply with the standards.

Drug content

Table 10 Percentage Drug content

S.No	Formulation	Drug content (%)
1	CF1	98.1±0.2
2	CF2	98.1±0.1
3	CF3	98.1 ±0.1
4	CF4	98.1±0.5
5	CF5	99.2±0.2
6	CF6	98.1±0.2

The formulations possessed almost nearing 100%, which indicated that there is no loss of drug during manufacturing or with additives.

Floating lag time & Floating time

The floating lag time is determined in order to assess the time taken by the dosage to float on the top of the dissolution medium, after placing the dosage form in the medium.

Table 11 Floating lag time & Floating time

S.NO	FORMULATION	FLOATING LAG TIME (sec)	FLOATING TIME (hrs)
1	CF1	42	6
2	CF2	120	5
3	CF3	122	8
4	CF4	35	7
5	CF5	45	8
6	CF6	122	7

In vitro release

Table 12 *In vitro* release for CF1 – CF6

	% DRUG RELEASE					
Formulations/	**CF1**	**CF2**	**CF3**	**CF4**	**CF5**	**CF6**
Time (h)						
0	0	0	0	0	0	0
0.5	12.31± 0.11	12.63± 0.12	23.33± 0.12	17.95± 0.31	12.92± 0.13	17.11± 0.31
1	16.22± 0.12	24.93± 0.14	42.53± 0.15	22.76± 0.16	23.72± 0.31	21.41± 0.21
2	24.93± 0.13	32.15± 0.12	63.15± 0.15	39.37± 0.31	36.62± 0.31	36.11± 0.31
4	38.11± 0.21	44.32± 0.13	62.83± 0.11	45.44± 0.12	46.83± 0.66	42.32± 0.23
6	45.51± 0.31	53.64± 0.23	69.43± 0.45	57.43± 0.21	67.36± 0.12	58.73± 0.34
8	53.66± 0.21	56.15± 0.35	71.23± 0.24	73.36± 0.26	80.39± 0.12	71.45± 0.24
16	66.42± 0.21	62.16± 0.21	84.35± 0.33	91.53± 0.33	93.13± 0.21	87.97± 0.12
24	69.22± 0.36	66.33± 0.12	89.63± 0.41	92.33± 0.21	99.12± 0.43	93.19± 0.55

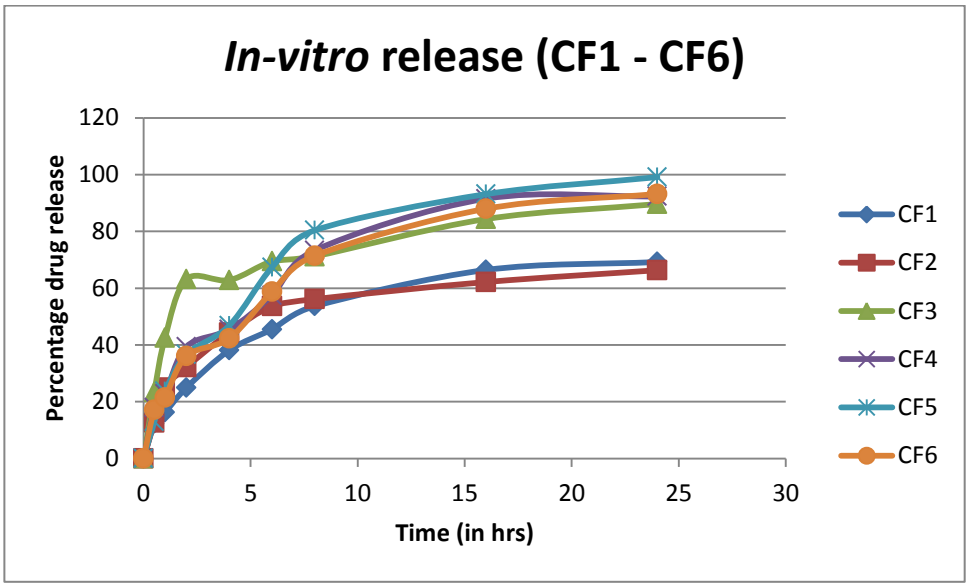

Fig 8 *In vitro* release for CF1 – CF6

From the in vitro release studies the trials CF1, CF2, CF3, CF4, CF5 and CF6 percent release was found to be 69.22±0.36, 66.33±0.12, 89.63±0.41, 92.33±0.21, 99.12±0.43, and 93.19±0.55 respectively. From the *in vitro* release results it was found that the trial CF5 was best amongst the trials.

7. SUMMARY AND CONCLUSION

Oral delivery of drugs is one of the most preferable routes of delivery due to the ease of administration, patient compliance and flexibility in formulation etc.

Floating systems significantly extend the period of time, over which drug may be released and prolongs dosing intervals and increase patient compliance. These systems retain in stomach and improve the absorption window and thus enhance the bioavailability.

Floating dosage forms are oral dosage forms of tablets, capsules, or micro beads and contain hydrocolloids that allow floating by swelling thereby prolong the residence time of dosage form within G.I tract.

Floating drug delivery or gastroretentive systems gastric emptying is an extremely variable process and ability to prolong and control the emptying time is a valuable asset for dosage forms, which reside in the stomach for a longer period of time than conventional dosage forms.

Floating drug delivery system (FDDS) could prolong GRT to obtain sufficient drug bioavailability . The system basically floats in the gastric fluid because of its lower density compared to that of the aqueous medium. FDDS is desirable for drugs with an absorption window in the stomach or in the upper small intestine.

Certain factors like density, size, shape, fast or fed conditions, nature of meal, age, posture, other drugs, biological factors may affect the gastric retention.

Candesartan cilexetil is a drug used in the treatment of hypertension. In the present project floating tablets were designed and executed.

Floating tablets of candesartan cilexetil were developed to prolong gastric residence time and to increase its bioavailability.

Six formulations (CF1 to CF6) of floating tablets of candesartan cilexetil were prepared by using individual and combination of polymers. HPMC, carbopol 934 and xanthum gum were used as polymer to retard the release of the drug in controlled manner.

Flow properties of the prepared granules for CF1 – CF6 were determined and it was found that the results were within the standard limits and specifications.

The floating tablets were prepared by direct compression method. Direct compression method is a suitable method for drugs which are sensitive to heat and moisture. Probably it saves the time also. In the present project the formulations were easily and quickly prepared because of the employment of direct compression.

The compressed tablets (CF1 – CF6) were evaluated for various tests quality control tests weight variation, content uniformity, friability, hardness, floating time, floating lag time and in vitro release studies.

The hardness and friability of the tablets (CF1 – CF6) were within the limits.

The weight variations of the tablets (CF1 – CF6) were found to be within the limits.

The content uniformity of the prepared tablets (CF1 – CF6) were within the limits.

The floating time and floating lag time for the prepared formulations (CF1 – CF6) was good.

From the in vitro release studies the trials CF1, CF2, CF3, CF4, CF5 and CF6 percent release at the end of the 24^{th} hour was found to be 69.22±0.36, 66.33±0.12, 89.63±0.41, 92.33±0.21, 99.12±0.43, and 93.19±0.55 respectively. From the *in vitro* release results it was found that the trial CF5 was best amongst the trials.

The formulation (CF5) with hydroxypropylmethyl cellulose and xanthum gum was found to be best formulation with floating time of 8 hrs and *in vitro* drug release of about 99.12±0.43% at the end of 24th hour.

CONCLUSION

The present work was based on the floating drug delivery of candesartan cilexetil. Floating tablets of candesartan cilexetil were formulated and evaluated. Based on the *in vitro* evaluation studies, optimized trial was found to be CF5 with good *in vitro* properties.

Hence it is ideal to formulate floating tablets for candesartan cilexetil.

However in future it is needed to carryout *in vivo* studies to implement candesartan cilexetil as commercial product.

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